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A facile and efficient ultrasound-assisted chlorosulfonic acid catalyzed one-pot synthesis of benzopyranopyrimidines under solvent-free conditions

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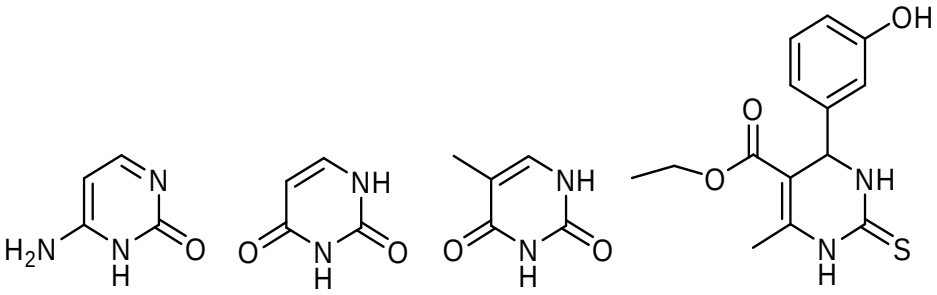
ABSTRACT

A facile and efficient ultrasound assisted Chlorosulfonic acid catalyzed one pot synthesis of benzopyranopyrimidines under solvent free condition via three-component condensation of 4-Hydroxy-coumarin with various substituted benzaldehydes and urea/thiourea was developed. This method gives the desired product in excellent yields in short reaction time with ease of work up.

Keywords: Multi-component reaction; Chlorosulfonic acid, Benzopyranopyrimidine; Ultrasound.

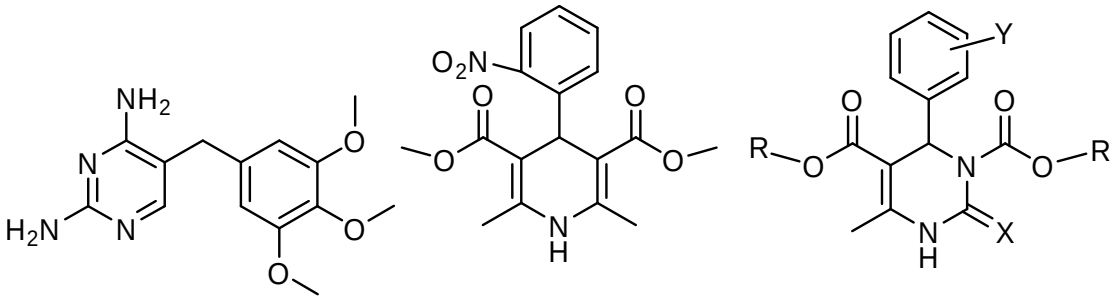
INTRODUCTION

The multicomponent coupling reactions are emerging as a useful source for building-up complex molecules with maximum simplicity and several levels of structural diversity. The development of environmentally friendly procedures in chemical and pharmaceutical industries has become a crucial and demanding research area in modern organic Chemistry [1]. Therefore, there has been considerable interest in green synthesis involving environmental benign catalyst and solvent. When solvent must be used, water is most acceptable in terms of cost and environmental impact. However, despite its large liquid range and extremely high specific heat capacity, it is frequently overlooked as a solvent for organic reactions. Most catalysts and reagents are deactivated or decomposed in water and in general, organic compounds are insoluble in water. Therefore, carrying out organic reactions in water poses important challenges in the area of reaction design. Multicomponent reactions (MCRs) have recently received the attention of organic chemists because of the many advantages of these reactions offered over conventional multi-step synthesis as well as their potential applications in medicinal chemistry for the generation of diverse scaffolds and combinatorial libraries for drug development [2-4]. One prominent MCR that produces an interesting class of nitrogen heterocycles is the venerable Biginelli dihydropyrimidine or pyrimidines synthesis. The Chemistry of pyrimidines and their derivatives has been studied for over a century due to the association of these systems with a variety of biological properties. They have been reported as antibacterials [5], antiviral and antitumor [6] agents. A number of heterocyclic fused pyrimidines or dihydropyrimidinones (DHPMs) are well known for their wide range of bioactivities and their applications in the field of drug research have stimulated the invention of a wide range of synthetic methods for their preparation and chemical transformations. Out of the five major bases in Nucleic acids three are pyrimidine derivatives which comprises of Cytosine **1** which is found in DNA and RNA, Uracil **2** in RNA and Thymine **3** in DNA. Because of their involvement as bases in DNA and RNA, they have become very important in the world of synthetic organic chemistry. Aryl-substituted 3, 4-dihydropyrimidin-2(1H)-one and their derivatives are an important class of substances in organic and medicinal chemistry [7].



1 Cytosine **2** Uracil **3** Thymine **4** Monastrol

Several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources, which also exhibit interesting biological properties [8]. Most notably, among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors. The scope of this pharmacophore has been further widening with their identification of 4-(3-hydroxyphenyl)-2-thione derivative **4** called monastrol [9] as a novel cell-permeable molecule for the development of new anticancer drugs. Monastrol **4** has been identified as a compound that specifically affects the cell-division (mitosis) by a new mechanism which does not involve tubulin targeting. It has been established that the activity of 4 consists of the specific and reversible inhibition of the motility of the mitotic kinesis, a motor protein required for spindle bipolarity. Trimethoprim **5** is a type of drug with a pyrimidine core which attacks the folic acid metabolism of bacteria and is often used as antibacterial agents [10]. 4-aryl-1, 4-dihydropyridines (DHPs) of the nifedipine type [11] (e.g. **6**) were first introduced into clinical medicine in 1975 and are still the most potent group of calcium channel modulators available for the treatment of cardiovascular diseases [12]. Dihydropyrimidines of type **7** (F show a very similar pharmacological profile, and in recent years, several related compounds were developed (e.g **7**) that are equal in potency and duration of antihypertensive activity to classical and second-generation dihydropyridine drugs [13].



5 **6** **7**

R=Alkyl, Y=NO_2, CF_3, X=O, S, NH

Trimethoprim Nifedipine Dihydropyrimidines

Some of the derivatives of dihydropyrimidines (DHPMs) are antihypertensive [14] antibacterial [15] -1a adrenoceptor- selective antagonists [16] and antioxidant agents [17]. Taking into account that coumarin derivatives themselves possess a variety of pharmaceutical properties [18], their fusion with pyrimidine fragment could give rise to compounds with enhanced biological activity. Although many synthetic strategies [19] have been applied for the preparation of fused pyrimidine derivatives, most of these methods suffer from some drawbacks including use of expensive reagents, drastic reaction conditions, long reaction time and laborious isolation procedures. We wish to report a simple multicomponent reaction and environment friendly protocol rather it is continuation of of our earlier work [20], in the present work, the tautomeric form of 4-Hydroxycoumarin, condenses with aldehydes and urea/ thiourea under solvent free condition at ambient temperature promoted by Chlorosulfonic acid catalysts under ultrasound irradiation and gives pyrimidines in excellent yields (Scheme 1). However, same reactions under thermal conditions requires longer reaction time and gives products in moderate to excellent yields.

Ultrasonication, based on cavitation effects leading to mass transfer improvement, is an important technique that is widely used today in organic synthesis and has a profound impact on the way chemists approach organic and parallel synthesis. Reductions in reaction times, improved yields and suppression of side products, relative to traditional thermal heating, are benefits of this technology. A large number of organic reactions can be carried out in higher yield, shorter reaction time and under milder conditions, by using ultrasonic irradiation [21]. Also, multi-component reactions (MCRs) are a very powerful tool for the construction of complex organic molecules by using readily available starting materials. MCRs have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion [22]. Environmental protection is a pressing need which requires chemical processes to be performed with higher yields, minimal expenses, and the use of non-toxic solvents, reagents, and catalysts.

EXPERIMENTAL SECTION

All reagents were purchased from Merck and Loba and used without further purification. Melting points were measured in open capillary and are uncorrected. The products were characterized by IR spectra and ^{1}H NMR. IR spectra were recorded on Perkin–Elmer FT-IR-1710 instrument. ^{1}H NMR was recorded on BrukerAC-200 MHz and Bruker MSL-300 MHz instrument using TMS as an internal standard. Elemental analyses were determined by an elemental analyzer (CHNS-O, EA 1108-elemental analyzer, Carlo Erba instruments). For ultrasound assisted organic reactions, ultrasonicator was used with the following technical specifications.

Electric supply: 230 v A.C. 50 Hz, 1phase.
Ultrasonic frequency: 36 ±3 KHz.
Ultrasonic power: 100 watts

General procedure:

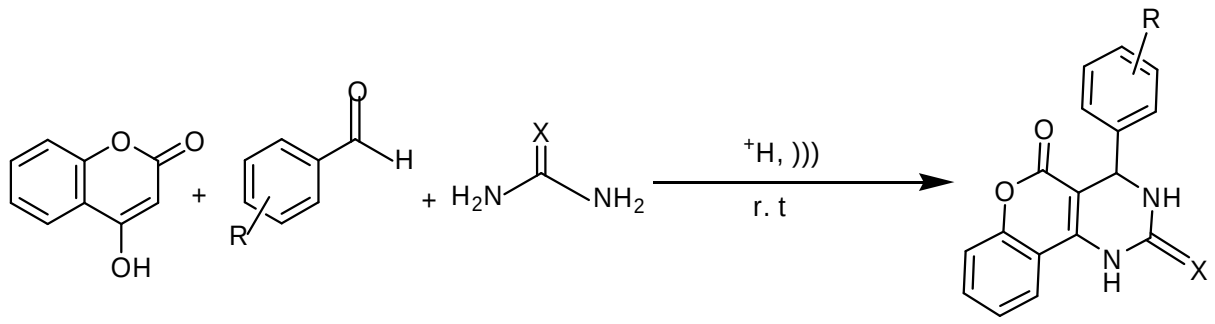
Conventional method (method A)

A mixture of 4-Hydroxycoumarin (1 mmol), aldehyde (1mmol), urea/thiourea (2 mmol) and 2.5% mol of Chlorosulfonic acid was added slowly and heated at 60^{o}C for appropriate time as mentioned in Table 1. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature and poured into ice water and the precipitated solid was collected by filtration, washed with ice cold water and dried. The crude product obtained was recrystallized from ethanol to give pure compound as white solid.

Ultrasound method (method B)

To a mixture of the 4-Hydroxycoumarin (1 mmol), aldehyde (1 mmol), urea/thiourea (2 mmol) and 2.5% mol of Chlorosulfonic acid was added slowly and the resulting mixture was irradiated in an ultrasound for the appropriate time (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and poured into crushed ice and stirred for 2-5 min. The crude product was collected by filtration under suction, washed with ice cold water and recrystallized from hot ethanol to afford pure benzopyranopyrimidines derivatives.

RESULTS AND DISCUSSION



8 **9** **10** **11**

R= H, Cl, OH, OMe, N (Me)$_2$, X= O, S

A new methodology is developed for the ultrasound promoted synthesis of benzopyranopyrimidines **11,** by 4-Hydroxycoumarin **8** acts as a cyclic *β*-keto ester condenses with aldehydes **9** and urea/ thiourea **10** under solvent free at ambient temperature, in the presence of chlorosulfonic acid ($ClSO_3H$) as a catalyst (Scheme1).

Scheme1.

Similar yields of product were obtained by carrying out the reaction at 60 ^{0}C using same catalyst. However these involved longer reaction time 30-60 min as compared to 5-25 min using ultrasound irradiation (Table 1, Method B).

Table 1: Synthesis of benzopyranopyrimidines using Chlorosulfonic acid as a catalyst

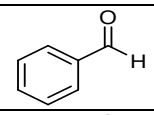
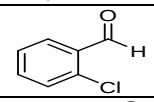
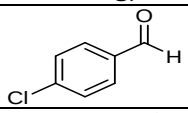
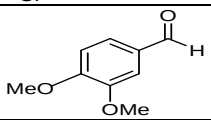
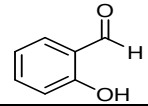
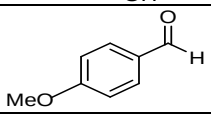
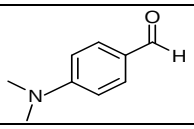
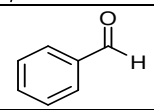
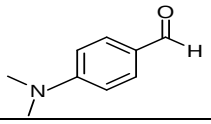
Entry	Substrate	X	Method A		Method B		M.P. ^{0}C	
			Time (min)	Yield (%)	Time (min)	Yield (%)	Obs.	Lit.
11a		O	30	92	5	96	160-162	162-164 [23]
11b		O	60	85	15	92	205-207	-
11c		O	40	95	10	94	198-200	197-198 [24]
11d		O	50	90	15	92	268-270	270-272 [23]
11e		S	40	91	20	93	169-171	-
11f		S	35	90	20	92	264-266	-
11g		O	45	90	20	92	239-241	240-242 [24]
11h		S	40	91	15	91	188-190	188-189 [23]
11i		S	50	85	25	92	232-234	234-236 [24]

Table 2: Comparison of catalytic activity of Chlorosulfonic acid with other catalysts (2.5mol %) for synthesis of 3, 4-Dihydro-4-Phenyl-1H-Chromeno [4, 3-d] Pyrimidine-2, 5-dione.

Entry	Catalysts (2.5 mol %)	Condition	Reaction Time (min)	Yield (%)
1	p-Toluenesulfonic acid	US	60	75
2	Methanesulfonic acid	US	30	80
3	Chlorosulfonic acid	US	5	96
4	Sulfuric acid	US	40	70
5	Boron trifloride	US	75	65

Further to optimize the reaction conditions different reactions were carried out by condensing 4-hydroxycoumarin, aromatic aldehydes and urea/ thiourea in presence of chlorosulfonic acid under ultrasound irradiation and solvent

free condition. The results are depicted in (Table 2). It is found that excellent yield of the desired product was obtained when Chlorosulfonic acid was used as a catalyst.

To evaluate the effect of catalyst concentration, condensation of 4-hydroxycoumarin, aromatic aldehydes and urea/ thiourea was cared out in presence of different amounts of catalyst (1, 2.5, 5, 7.5, 10 mol %) under solvent-free conditions (Table 3). It was observed that 2.5 mol % of Chlorosulfonic acid was an optimum amount for this reaction to furnish the desired product in excellent yield.

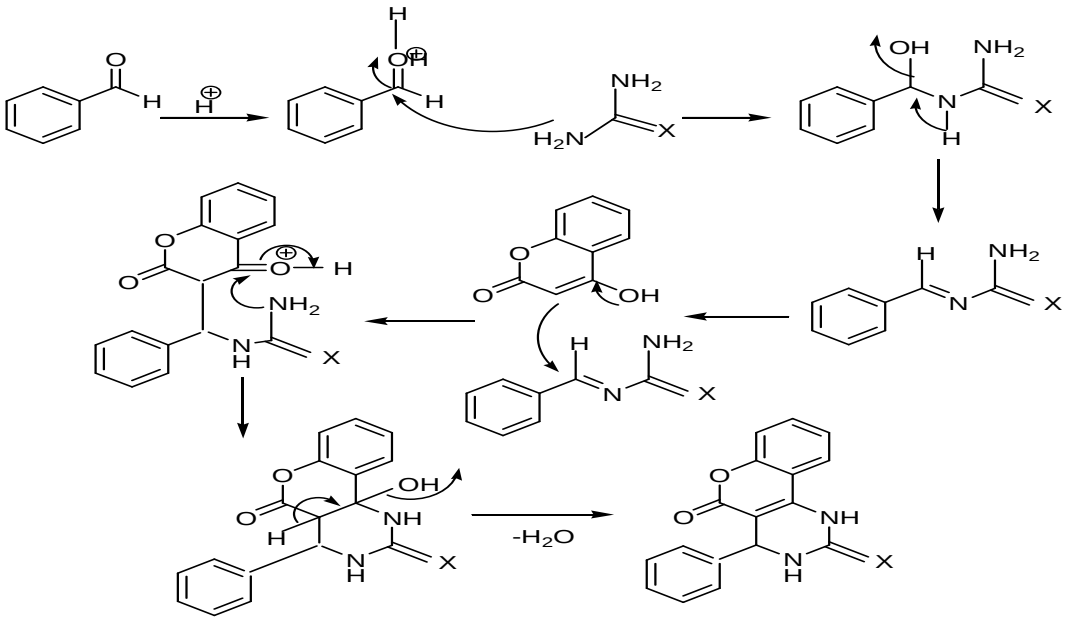
Table 3: Effect catalyst (Chlorosulfonic acid) concentration for the synthesis of 3, 3-Dihydro-4Phenyl-1-H-Chromeno [4,3-d] Pyrimidine-2, 5-dione

Entry	Catalyst concentration (mo %)	Time (min)	Yield (%)
1	1	15	67
2	2.5	5	96
3	5	5	82
4	7.5	5	60

Reaction condition: 4-hydroxy coumarin (1 mmol), benzaldehyde (1 mmol), and urea (2 mmol) at by varying the amount of catalyst under solvent free conditions using ultrasound irradiation.

A model reaction involving aldehydes **9**, 4-hydroxy coumarin **8** and urea/thiourea **10** and Chlorosulfonic acid ($ClSO_3H$) as a catalyst to afford the pyranopyrimidine derivatives **11** under various reaction conditions was performed for an appropriate time. The results are depicted in (Table 2).

Chlorosulfonic acid plays a complex role in accelerating the coupling reaction and thus promotes the formation of products (Scheme 2).



Scheme 2: A probable mechanism for the reaction

In order to evaluate and compare performance of Chlorosulfonic acid as a catalyst the condensation reaction of benzaldehyde, urea/thiourea with 4-hydroxy coumarin was carried out using some other catalysts such as P-TSA, phosphoric acid, phospomolybdic acid, sulfuric acid, iodine in different concentrations of aqueous medium (ethanol:water). The results are shown in Table 2. Further, to optimize the quantity of Chlorosulfonic acid as a catalyst the condensation reaction between benzaldehydes (1.0 mmol), 4-hydroxy coumarin (1.0 mmol), and urea /thiourea (2.0 mmol) was carried outunder solvent free condition using different mol% of Chlorosulfonic acid as a

catalyst. It is observed that highest yield is obtained using Chlorosulfonic acid 2.5 mol% under solvent free condition (Table 3).

Physical and Spectral data for all the compounds:

3, 4-Dihydro-4-phenyl-1H-chromeno [4, 3-d] pyrimidine-2, 5-dione (11a). White solid, m.p. 162-163 ^{0}C. IR: (KBr) (ν_{max} cm^{-1})= 3410, 2924, 2727, 2360, 1654, 1459, 1379, 1303, 1154, 1075, 964, 722 cm-$^{-1}$; ^{1}H-NMR (DMSO): δ(ppm)= 6.34(s, 1H, CH), 7.16-7.59(m, 9H, Ar-H), 7.87(brs, 1H, NH), 7.9(brs, 1H, NH); Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58%. Found**:** C, 69.92; H, 4.22; N, 9.70%.

4-(2-Chlorophenyl)-3, 4-dihydro-1*H*-chromeno [4, 3-*d*] pyrimidine-2, 5-dione (11b). White solid, m.p. 207-209 ^{0}C. IR: (KBr) (ν_{max} cm^{-1}) = 3402, 3300, 3040, 1682, 1607, 1159, 1219, 1060, 757, 652, 553, 493, 453 cm^{-1}; ^{1}H-NMR (DMSO): δ(ppm)= 6.14(s,1H,CH), 7.1-7.53(m, 8H, Ar-H), 7.84(brs,1H,NH), 7.86(brs,1H, NH); Anal. Calcd for $C_{17}H_{11}ClN_2O_3$: 62.49; H, 3.39; N, 8.57%. Found**:** C, 62.58; H, 3.51; N, 8.65%.

4-(4-Chlorophenyl)-3, 4-dihydro-1*H*-chromeno [4, 3-*d*] pyrimidine-2, 5-dione (11c). White solid, m.p. 197-198 ^{0}C. IR: (KBr) (ν_{max} cm^{-1}) = 3400, 3079, 2893, 2839, 2733, 2615, 1668, 1608, 1566, 1491, 1450, 1350, 1309, 1217, 1093, 1055, 1014, 765, 671 cm^{-1}; ^{1}H-NMR (DMSO): δ(ppm)= 6.45(s,1H, CH),7.28-7.66(m,8H,Ar-H),7.94(brs,1H,NH), 7.98(brs,1H,NH); Anal. Calcd for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57%. Found: C, 62.55; H, 3.47; N, 8.66%.

3,4-Dihydro-4-(3,4-dimethoxyphenyl)-1H-chromeno[4,3-d]pyrimidine-2,5-dione (11d). White solid, m.p. 270-272 ^{0}C. IR: (KBr) (ν_{max} cm^{-1}) = 3415, 2938, 2835, 2728, 2611, 2363, 1699, 1617, 1506, 1453, 1346, 1244, 1187, 1126, 1010, 907, 763, 506, 452 cm$^{-1;1}$H-NMR(DMSO):δ(ppm)= 3.54(s,3H,OCH_3),3.69(s,3H,OCH_3),6.25(s,1H,CH),6.64-7.86(m,7H, Ar-H), 7.88 (brs,1H,NH), 7.89(brs,1H,NH); Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95%. Found: C, 64.73, H, 4.69; N, 7.99%.

1, 2, 3, 4-Tetrahydro-4-(2-hydroxyphenyl)-2-thioxochromeno [4, 3-d] pyrimidin-5-one (11e). Pale yellow, m.p. 169-171 ^{0}C. IR: (KBr) (ν_{max} cm^{-1}) = 3411, 3071, 2362, 1752, 1606, 1488, 1449, 1389, 1343, 1241, 1271, 1039, 940, 865, 752, 465 cm^{-1}; ^{1}H-NMR (DMSO): δ(ppm)= 3.3(brs,1H,OH), 6.89-7.85(m,9H,Ar-H), 8.32(brs,1H,NH), 10.67(brs,1H,NH); Anal. Calcd for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64; S, 9.89%. Found: C, 63.07; H, 3.84; N, 8.73; S, 9.91%.

1, 2, 3, 4-Tetrahydro-4-(4-methoxyphenyl)-2- thioxochromeno [4, 3-d] pyrimidin-5-one (11f). White solid, m.p. 265-267 ^{0}C. IR: (KBr) (ν_{max} cm^{-1}) = 3401, 3072, 1967, 1714, 1626, 1608, 1583, 1489, 1450, 1330, 1344, 1344, 1242, 1217, 1174, 1039, 941, 866, 808, 754, 678, 624, 464 cm^{-1}**;** ^{1}H-NMR (DMSO): δ(ppm)= 3.78(s, 3H,OCH_3), 6.43(s,1H,CH), 6.86-7.71(m,8H,Ar-H), 8.02(brs, 1H, NH), 8.06(brs,1H, NH); Anal. Calcd for $C_{18}H_{14}N_2O_3S$: C, 63.89; H, 4.17; N, 8.28; S, 9.48%. Found: C, 63.96; H, 4.26, N, 8.38; S, 9.53%.

4-(4-(Dimethylamino) phenyl)-3, 4-dihydro-1H-chromeno [4, 3-d] pyrimidine-2, 5-dione (11g). Pinkish brown, m.p.180-182 ^{0}C. IR: (KBr) (ν_{max} cm^{-1}) = 3426, 3088, 2885, 2727, 2609, 1662, 1610, 1568, 1523, 1450, 1348, 1307, 1207, 1184, 1089, 1053, 958, 906, 765, 744 cm-1**;** ^{1}H-NMR (DMSO): δ(ppm)= 3.19(s,6H,CH_3),6.44(s,1H,CH), 7.24-7.37(m,8H,Ar-H), 7.86(brs,1H, NH),7.90(brs,1H,NH); Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53%. Found**:** C, 68.13; H, 5.18; N, 12.60%.

1, 2, 3, 4-Tetrahydro-4-phenyl-2-thioxochromeno [4, 3-d] pyrimidin-5-one (11h). White solid, m.p.188-189 ^{0}C. IR: (KBr) (ν_{max} cm^{-1}) = 3450, 2923, 2854, 1656, 1463, 1377, 1303, 1155, 970, 727 cm^{-1}**;** ^{1}H-NMR (DMSO): δ(ppm)= 6.36(s,1H,CH), 7.17-7.60 (m, 9H,Ar-H), 7.88(brs,1H,NH), 7.91 (brs, 1H, NH); Anal. Calcd for $C_{17}H_{12}N_2O_2S$: C, 66.22; H, 3.92; N, 9.08;S, 10.40 %. Found**:** C, 66.31; H, 3.95; N, 9.13; S, 10.44%.

4-(4-(Dimethylamino) phenyl)-1, 2, 3 4-tetrahydro-2-thioxochromeno[4,3-d] pyrimidine-5-one (11i). Pinkish brown, m.p. 234-236 ^{0}C. IR: (KBr) (ν_{max} cm^{-1}) =3426, 3088, 2885, 2727, 2609, 1662, 1610, 1568, 1523, 1450, 1348, 1307, 1207, 1184, 1089, 1053, 958, 906, 765, 744 cm-1**;** ^{1}H-NMR (DMSO): δ(ppm)= 3.61 (brs, 6H, N (CH_3)$_2$), 6.01 (s, 1H, 4-H), 7.20–8.01 (m, 8H, Ar-H), 11.40 (brs, 2H, 2NH, D_2Oexchangeable): Anal. Calcd for $C_{19}H_{17}N_3O_2S$: C, 64.95; H, 4.84; N, 11.96%. Found: C, 64.92; H, 4.86; N, 11.98%.

CONCLUSION

In conclusion, we have developed extremely efficient methods for the synthesis of pyranopyrimidines under ultrasound irradiation in solvent free condition at ambient temperature using Chlorosulfonic acid which simultaneously catalyzes the reaction and solublizes the reactants This method has several unique merits, such as high yields, relatively short reaction times, the use of small amount of the catalyst, simple procedure, low cost . To put it differently, the method significantly contributes to the practice of green chemistry.

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